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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/841,843	04/25/2001	Jurgen Bode	BOET 0130 PUS	6703

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EXAMINER	
WOITACH, JOSEPH T	
ART UNIT	PAPER NUMBER
1632	9

DATE MAILED: 09/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary	Application N .	Applicant(s)	
	09/841,843	BODE ET AL.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this c mmunication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-11* is/are pending in the application.

4a) Of the above claim(s) *7-9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,10 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *09/257,561* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This application filed April 25, 2001, is a continuation of application 09/257,561, filed February 25, 1999, now abandoned, which claims benefit to foreign application 98 103 490.3 filed February 27, 1998 with the EPO.

Applicants amendment filed June 18, 2003, paper number 8, has been received and entered. The abstract has been amended. Claim 5 has been canceled. Claims 1, 10, and 11 have been amended. Claims 1-4, 6-11 are pending.

Election/Restriction

Applicant's election of Group I, claims 1-6, 10 and 11 in Paper No. 6 was acknowledged. Because, the election and was treated as an election without traverse because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement (MPEP § 818.03(a)). Applicant has not provided any new arguments, therefore the restriction is maintained for the reasons of record.

Claims 1-4, 6-11 are pending. Claims 7-9 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 6. Claims 1-4, 6, 10 and 11 are currently under examination.

Specification

The abstract of the disclosure objected to because it contains terms which are not permitted is withdrawn.

The amendments to the abstract has obviated the basis of the objection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 10 stands rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for use of a FLP/frt recombinase system in a mouse embryonic stem cell comprising the specific method steps set forth in claim 1 for the generation of a transgenic mouse, does not reasonably provide enablement for use of embryonic stem cells from other vertebrates for the generation of transgenic vertebrates. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Initially, it is noted that claims 1-4, 6 and 11 have been removed from the rejection. With respect to claim 6 it is noted that the claimed as amended to be dependent on claim 1 specifically recites that the embryonic stem cell is a mouse embryonic stem cell and thus, is within the enabled scope set forth in the basis of the rejection. Similarly, claim 11 is drawn to generating

transgenic mice with the cells of claim 1 and to the extent that mouse embryonic stem cells must be used to generate the transgenic mouse this embodiment is also within the scope of enablement set forth in the basis of the rejection. With respect to claims 1-4, it is noted that the claims have been amended for the use of any embryonic stem cell and in particular, the embodiment that the embryonic stem "can regenerate to [a] complete organism" (claim 1) has been deleted. To the extent that the vectors can be successfully used in any cell type as demonstrated in Schlake and Bode, Examiner would agree that the deletion of the limitation requiring that the embryonic stem cell give rise to an intact organism has obviated the basis of the rejection over these claims. It is noted that the basis of the rejection is still valid, however the single use of the cells for the generation of an intact organism would be considered a recognized single non-enabled embodiment or limitation for the use of the resulting embryonic stem cell. However, claim 10 requires the generation of a transgenic vertebrate comprising the use of the embryonic stem cell generated in the method of claim 1, therefore it is subject to the limitations and/or availability of known embryonic stem cells at the time of filing.

Applicants note the publication dates of the references used in establishing the basis of the rejection and argue 'a person skilled in the art is completely aware that embryonic stem cells were not only available from the mouse but also from other animals' (page 9). See Applicants' amendment, pages 8-9. Applicants arguments have been fully considered, but not found persuasive.

Examiner would agree that embryonic stem cells from other mammals other than mice have been isolated, however none of the ES cells have been demonstrated to be totipotent or used successfully to generate a transgenic animal. The date of the references used in the basis of the rejection is not material to the basis of the rejection because while other ES cells have been subsequently isolated since the effective filing date of the instant application, the limitations of the cells not being totipotent nor capable of giving rise to a complete transgenic vertebrate as discussed by both Seamark and Moreadith *et al.* is still a recognized limitation of embryonic stem cells from species other than mice even today. Based on the evidence of record, the only embryonic stem cell which could be successfully used in the method set forth in claim 10 would be those isolated from mice. As noted above, Examiner does not contend that the vector system would not be functional in any type of cell, rather the basis of the rejection focuses on the art recognized limitation of embryonic stem cells known and characterized in the art. The present disclosure provides no specific guidance for the isolation and culturing of embryonic stem cells and relies on art recognized methodology. Since the claimed invention requires and relies on teachings known in the art to practice the claimed invention, it is also subject to art recognized limitations. 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). In the instant case, the only embryonic stem cells capable of giving rise to a complete transgenic mammal known and characterized in the art are from the mouse. Given the complexity of isolating and characterizing embryonic

stem cells and the lack of any specific guidance, it would constitute undue experimentation to practice the claimed invention in the full breadth of the claim.

Thus, in view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed. Therefore, for the reasons above and of record the rejection is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 6, 10 and 11 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn.

The amendments to the claims have obviated the basis of each of the specific rejections.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 6 stand rejected under 35 U.S.C. 102(b) as being anticipated by Schlake *et al.* (Biochemistry, 1994).

Applicants summarize the basis of the rejection, reviewing the general teaching of Schlake *et al.* and argue that Schlake *et al.* explicitly decide not to use embryonic stem cells because of art recognized drawbacks and reduce to practice instead an established cell line which has lost its ability to affect homologous recombination as compared to embryonic stem cells (pages 9-10). Further it is argued that Schlake *et al.* do not teach step (b) of claim 1 for 'selecting cell clones surviving the conditions for positive selection' citing relative passages of Schlake *et al.* (pages 10-11 and claim 1(b)). See Applicants' amendment, pages 9-11. Applicants' arguments have been fully considered, but not found persuasive.

Initially, it is noted that Applicants do not argue that the vector system used by Schlake *et al.* is different from that disclosed and claimed in the present specification. A comparison of the specific positive and negative markers and specific recombinase sites reduced to practice in both the present disclosure and Schlake *et al.* indicate the vector and methodology used for selecting exchanged sequences are the same. With respect to Applicants' arguments that Schlake *et al.* do not teach step (b) of claim 1, it is noted that step (b) simply requires selecting clones under positive selection. The passage pointed to by Applicants teach that the BHK cells containing the selectable marker 'were cultured continuously for 4 weeks' which would clearly provide for BHK clones having the polynucleotides for the positive selection. There are no limitations in the instant claims for selecting cells which would provide any different result than that taught by

Schlake *et al.* It may be that Applicants are implying that Schlake *et al.* do not indicate to provide single isolated clones however this is not specifically recited or required by the instant claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In this case Applicants' argument that the references fail to show certain features of applicant's invention is not persuasive because the claims do not require these specific features.

With respect to Applicants' arguments that Schlake *et al.* teach not to use embryonic stem cells and reduce to practice only other types of established cell lines which have a believed reduction in the capacity for homologous recombination Examiner notes there is no specific teaching away in Schlake *et al.* from using embryonic stem cells nor specific teaching that embryonic stem cells have characteristics or limitations which would make them non-functional in the current methods. Schlake *et al.* teach that the skilled artisan uses embryonic stem cells for targeted integration and it is well known in the art that mouse embryonic stem cells are used in the generation of transgenic mice. Again, there is no teaching in Schlake *et al.* that embryonic stem cells would not work in the instantly claimed method, and it seems that Applicants are relying on the fact that Schlake *et al.* chose to reduce to practice the claimed invention in a cell type which would be less effective in homologous recombination. Applicants' arguments are not found persuasive because Schlake *et al.* discuss the use of targeted homologous recombination in embryonic stem cells and there is no specific teaching of limitations or characteristics taught to

using embryonic stem cells which would prohibit there use in the instantly claimed method.. Moreover, since embryonic stem cells may be expected to have an increased capacity for recombination they may provide increased efficiency of the method.

Therefore, because Schlake *et al.* teach each limitation encompassed by the instantly claimed method and because there is no teaching away specifically taught by Schlake *et al.* or recognized in the art for using embryonic stem cells for targeted recombination, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 10 and 11 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Schlake *et al.* in view of Jung *et al.*

Claims 1, 10 and 11 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Schlake *et al.* in view of Ludwig *et al.*

Applicants summarize the basis of the rejections and outline the requirements for making a *prima facie* case of obviousness (pages 11-13). Applicants argue that Schlake *et al.* 'clearly states to not use embryonic stem cells but rather suggests to use established cell lines like BHK or CV-1 cells due to their known advantages' (bottom of page 13). Further, because of this negative teaching by Schlake *et al.* one of skill in the art would not combined the teaching of Jung *et al.* and/or Ludwig *et al.* for the generation of a transgenic mouse, and that the methods taught by Jung *et al.* and Ludwig *et al.* are different from those instantly claimed. Finally, Applicants argue that the presently claimed invention provides surprising results which could not have been predicted by the work of Schlake *et al.* (pages 13-14). See Applicants' amendment, pages 11-14. Applicants' arguments have been fully considered but not found persuasive.

As noted above, the vector system taught by Schlake *et al.* is the same as reduced to practice in the instant disclosure and the methods taught by Schlake *et al.* anticipate each of the limitations set forth in claim 1. Further, it is well known in the art that mouse embryonic stem cells are routinely used for targeted recombination and subsequently used to generate transgenic mice. The teaching of Jung *et al.* and Ludwig *et al.* is relied upon for the specific methodology required for generating transgenic mice and as evidence that known recombinases are used and

functional within this context. Applicants' arguments are not found persuasive because the teaching of Schlake *et al.* anticipates claim 1 and the use of embryonic stem cells. Moreover, the routine use of mouse embryonic stem cells for the targeted recombination of a gene of interest for the specific purpose of generating the transgenic mouse. As noted by Applicants Examiner agrees that the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art *(In re McLaughlin,* 443 F.2d 1392, 170 USPQ 209 (CCPA 1971)). However, for the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references (*In re Nilssen*, 7 USPQ2d 1500 (Fed. Cir. 1988)). In the instant case, at the time of filing the use of use of mouse embryonic stem cells for the generation of transgenic mice was well known and routine. Additionally, positive/negative selection vectors and methods using these vectors were routinely used for affecting homologous recombination in embryonic stem cells. Further, the use of recombinases in the targeting vectors and resulting cell were also used. Given the teaching by Schlake *et al.* that the vectors and methods taught therein provide methodology for targeted recombination which is effective in cells which are perceived to have a lower capacity for homologous recombination than embryonic stem cells provides clear motivation for using this more effective methodology. Moreover, the successful results of each of references provide a clear expectation of success. With respect to Applicants' arguments that the methods provide surprising results is unpersuasive because they would be anticipated and inherent over claim 1 as argued above in the

rejection made under 35 USC 102(b). Further, even if there was an unexpected result in light of the teaching of Schlake *et al.* there is no limitation in the claim to differentiate the claimed invention from that made obvious by the prior art. Note that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See *In re O'Farrell*, 7 USPQ2d 1673 (CAFC 1988). Moreover, once a embryonic stem cell is generated by the methods of claim 1, any potential unexpected result for increased efficiency of making the cell would not extend to the use of the cell. More specifically a transgenic embryonic stem cell made by any means would function the same way in the breadth and context of claimed invention set forth broadly in claims 10 and 11. Applicants' arguments are not found persuasive because Schlake *et al.* anticipate the methods of claim 1, and the use of mouse embryonic stem cells for the generation of transgenic mice would have been obvious and would have had a high expectation of success for this use.

Therefore, for the reasons stated above and in the previous office action the rejections are maintained.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Deborah D Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630

Joseph T. Woitach